Fish anesthetics in Norway

Use and properties of isoeugenol, tricaine, benzocain and metomidate

FGB course, Tuesday 6th March 2018, University of Bergen, Norway

Lars Speilberg - DVM PhD - Scanvacc AS

Scanvacc AS

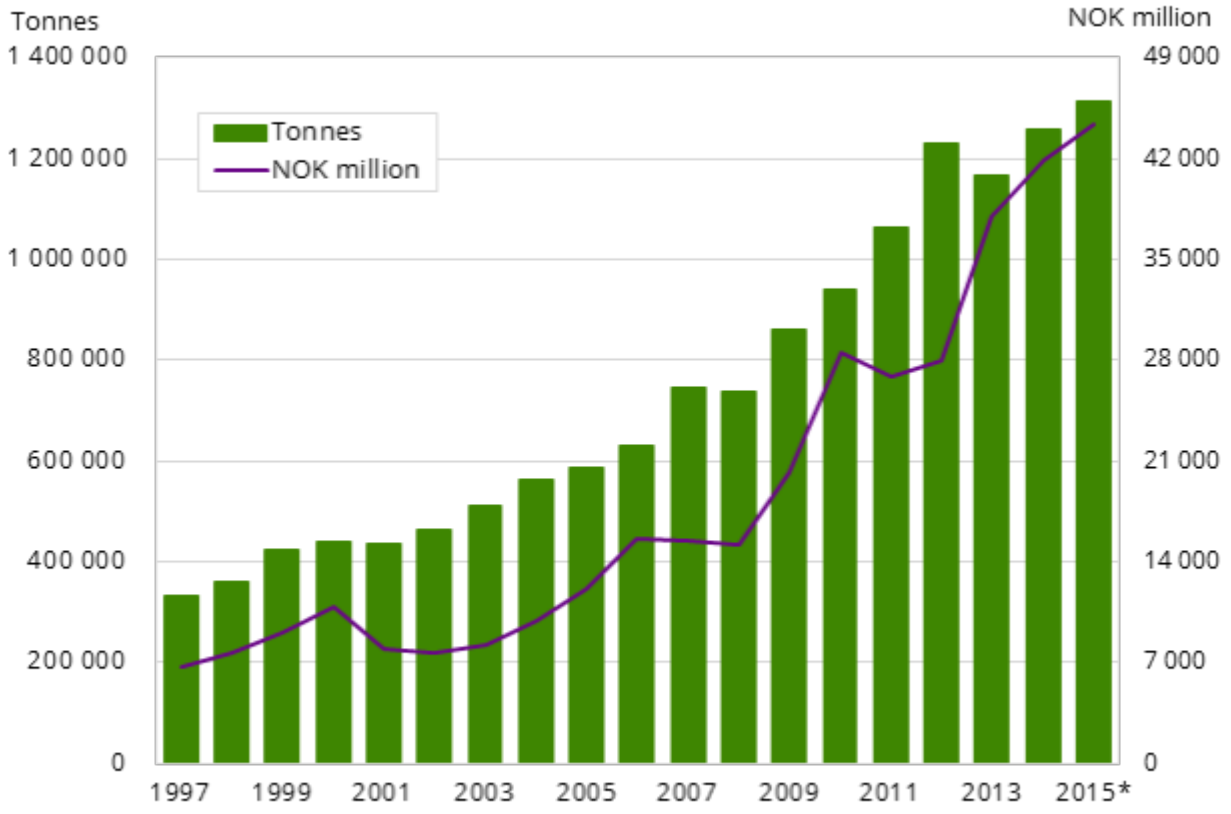
- Norwegian pharmaceutical company
  www.scanvacc.com

- Run by 3 vets:
  - Ole Kristian Kaurstad
  - Jon Inge Erdal
  - Lars Speilberg

- Anaesthetics:
  - Aqui-S vet. (isoeugenol) - sedative
  - Finquel vet. (tricaine) – anaesthetic
  - Aquacalm vet. (metomidate) - anaesthetic

Norwegian fish farming

Figure 1. Sales of salmon. Quantity and first hand value



Source: Statistics Norway.

Norwegian fish farming

2015:

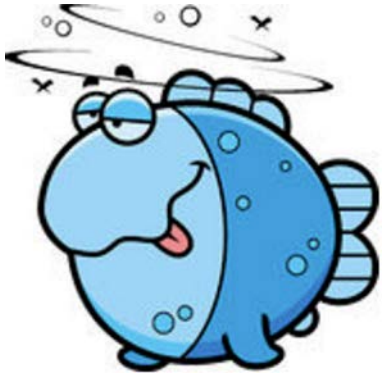
- 1 303 000 tonnes Atlantic salmon
- 73 000 tonnes rainbow trout
- 1 244 tonnes Atlantic halibut

Cleaner fish:

- 13 385 000 lumpfish
- 1 340 000 wrasse

Sedation and anaesthesia – areas of use in Norway

Sedation



During stressful fish handling, typically crowding and pumping:

- Smolt delivery and transport
- Bath treatments in tanks, well boats or pens
- Brood stock handling
- Premedication to anaesthesia

Anaesthesia

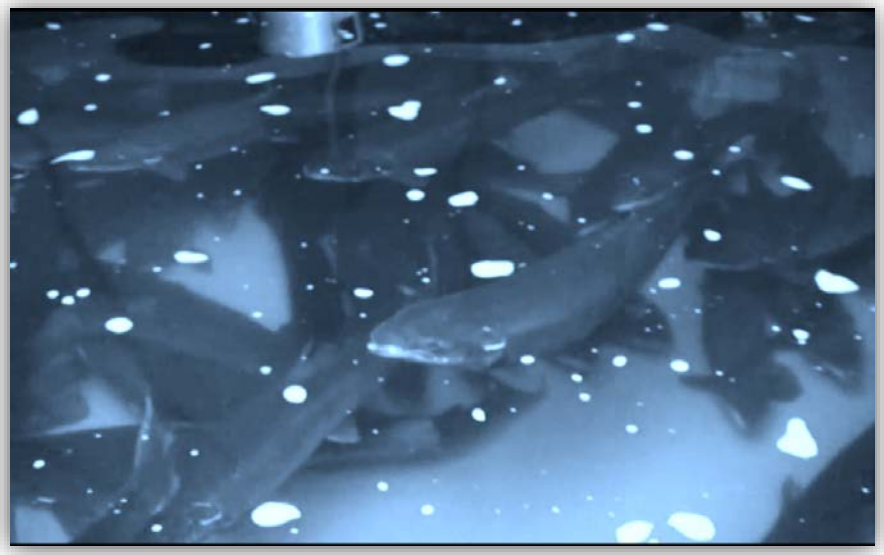
- Vaccination
- Sea lice counting
- Brood stock handling
- Research purposes
- Euthanasia

Sedation

"Calming effect achieved by using anaesthetics in low doses"

Used to:

- Reduce stress and stress related disease
- Facilitate handling
- Improve fish welfare



Sedation

Substances used for sedation:

- Isoeugenol
  - «Aqui-S vet.»

In theory also

- *Tricaine*
  - *«Finquel vet.»*
  - *«Tricaine Pharmaq»*
- *Benzocaine*
  - *«Benzoak vet.»*

Aqui-S vet.

- Anaesthetic, used in low doses for sedation
- Fluid concentrate
- Active ingredient isoeugenol (50 %) + emulsifier
- Stem solution 1 : 10
- Norwegian MA since 2013 – approved for use on food fish
  - Withdrawal time 2 degree days
- Sales in 2016
  - 20 000 litres
  - Corresponding to sedation of approximately 100 million fish

Aqui-S vet.

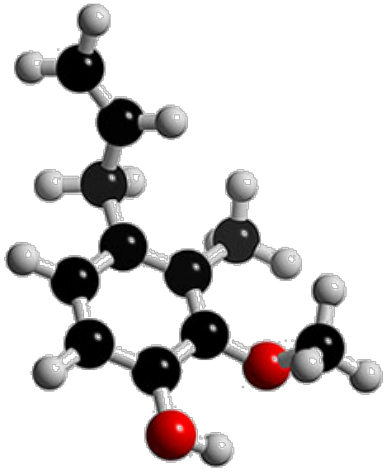
Isoeugenol

- Derived from clove oil
- Naturally occurring in food
  - Spices, smoked food, beer (!)
- Used as a feed additive (GRAS)
  - Flavouring agent
- Local anaesthetic in human dentistry

Aqui-S vet.

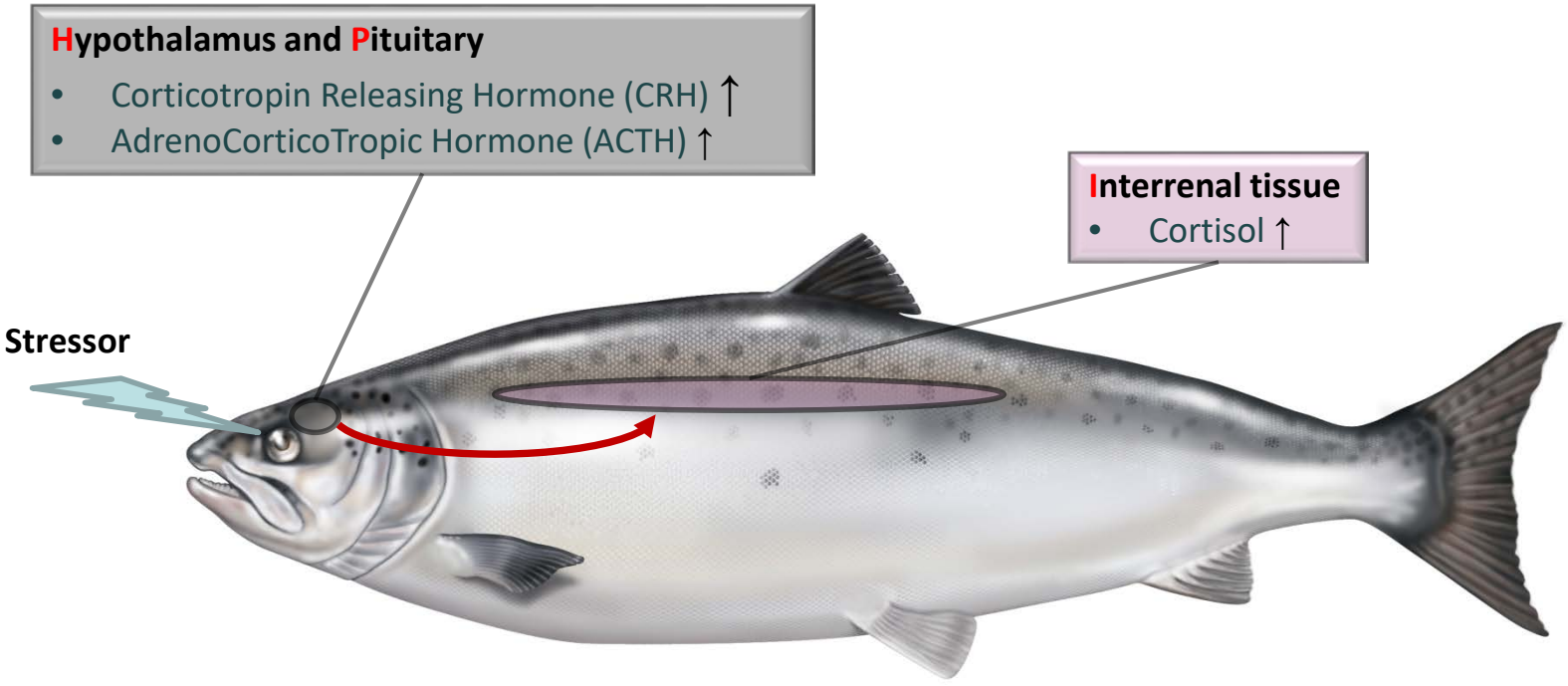
Pharmaceutical properties of isoeugenol:

- Slow acting – (5-15 min)
- Typical dose 2,5 mg/L (5 ml Aqui-S/m^3)
- Impacts behaviour without loss of swimming ability or equilibrium
  - Less swimming activity during stress, less O_2-consumption and CO_2-production
  - Reduces fear and flight
- Believed to be analgesic
- Good stress reducing capacity; moderates the stress response at subsequent handling



2-Methoxy-4-prop-1-enyl-phenol

Stress physiology - «The HPI-axis»
Hypothalamic → Pituitary → Interrenal axis



- Isoeugenol reduces cortisol rise by interfering high up in the HPI-axis, on stressor perception.
- Mechanism of action unclear. Nicotine receptors? Sodium channels?

Apropos;
stress reducing capacity of a drug

- All anaesthetics will elicit a stress response and cortisol rise in the fish, especially following exposure to full anaesthetic dose

- A slow acting anaesthetic will tend to induce more stress, as the fish will sense the anaesthetic and struggle against sleep for a longer period of time

- **It is important to differentiate the stress reduction capacity of a drug used in low doses as a sedative from this phenomena!**

One example:

Stress reducing capacity of a drug;

1. **100 ml Aqui-S/m^3**
   Isoeugenol used 4 times the max recommended dose will put the fish (permanently) to sleep in less than 1 minute, and no cortisol will have time to be produced

2. **25 ml Aqui-S/m^3**
   Isoeugenol used with the recommended dose as an anaesthetic will need 5-15 minutes to put the fish to sleep, plenty of time to elicit a significant cortisol rise

3. **5 ml Aqui-S/m^3**
   Isoeugenol used in recommended dose as a sedative will need 5-15 minutes to sedate the fish, but the low concentration elicits only a minor cortisol rise

   The cortisol rise caused by subsequent handling will however be significantly reduced compared to non-sedated fish. This is the true stress reducing capacity of a drug.

Sedation with Aqui-S

- General impact on behaviour (5 ml/m^3)

Scanvacc
FOCUSED ON FISH WELFARE

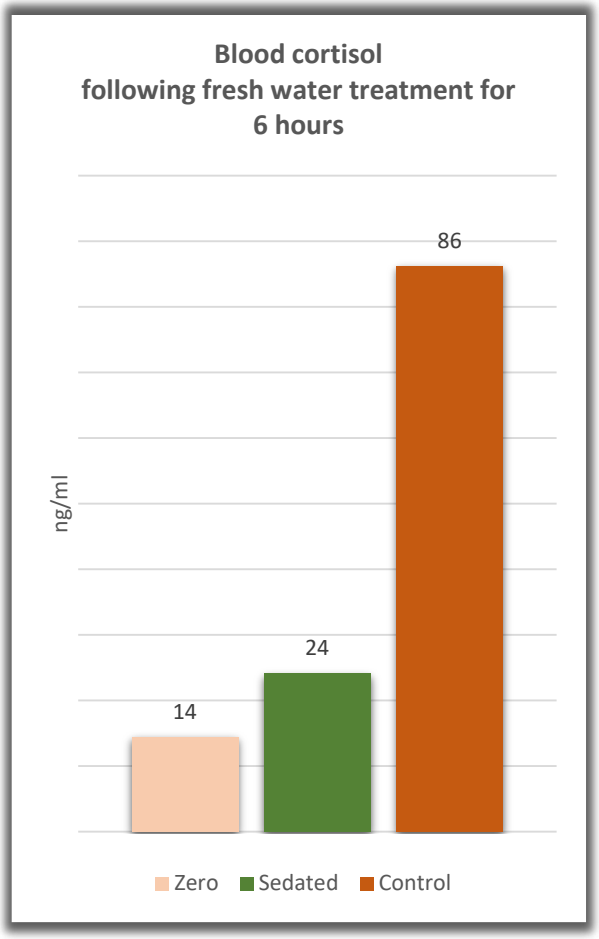
Scanvacc
FOCUSED ON FISH WELFARE

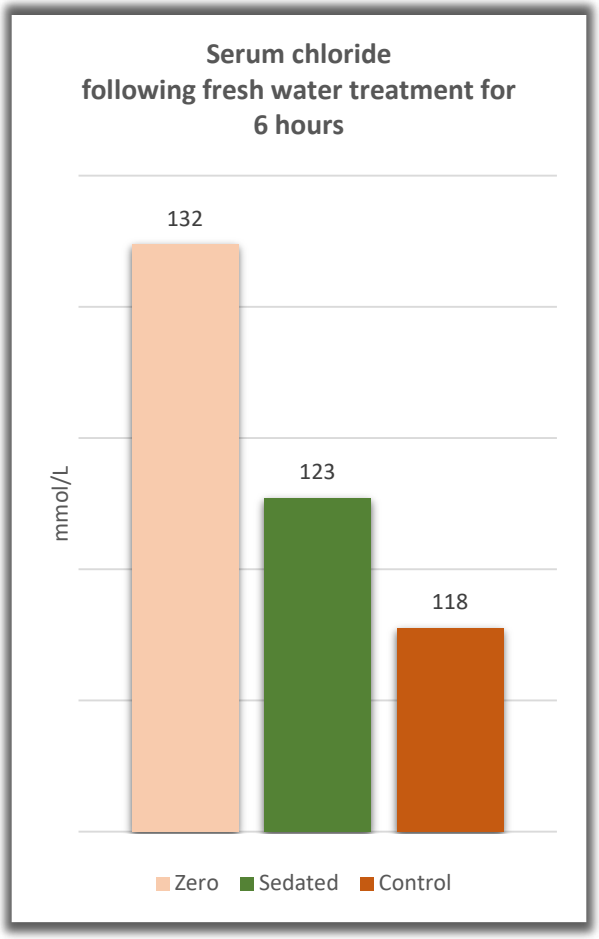
Sedation during bath treatments

- During treatments against sea lice or AGD
- Especially when using H_2O_2 or fresh water
- In well boats or cages (enclosed, full tarpaulin)

- Reduces stress
  - less panic (flight reactions)
  - reduced uptake of topical sea lice drugs
  - reduced loss of salts during fresh water treatments

Controlled trial – Letsea Sandnessjøen – May 2017





Sedation during bath treatment

Sedation during brood stock sorting

- Stress reduction (for fish and personnel)
  - Fish up to 18 kg!

Anaesthesia

- Vaccination
  - Ca. 350 million fish pr. year in Norway
  - Precision work
  - Immobilisation is crucial

Vaccination

Anaesthesia

- Sea lice counting
  - Ca. 1,25 million fish counted pr. year

Anaesthesia

- Brood stock handling
  - Grading
  - Pit-tagging
  - Tissue sampling

Anaesthesia

Substances:

- Tricaine
  - «Finquel vet.»
  - «Tricaine Pharmaq»
  - «Nytox vet.»
- Benzocaine
  - «Benzoak vet.»
- Metomidate (not food fish)
  - Aquacalm

To some extent (sea lice counting, research)

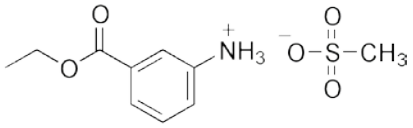
- *Isoeugenol*
  - *«Aqui-S»*

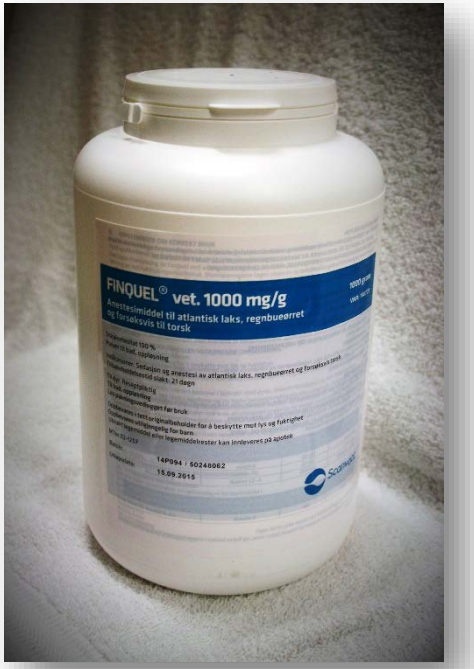
Substance	Sales 2016 (Kg active)
Tricaine	5447
Benzocaine	1400
Metomidate	< 1

Anaesthesia for vaccination

Finquel vet. / Tricaine Pharmaq / Nytox vet.

- Tricaine powder 1000 mg/g
- Synonyms:
  - Metacaine
  - MS222
  - Tricaine mesilate
  - Tricaine methane sulphonate ++
- Fast induction & recovery
- Analgesic
- SPC: doses up to 135 mg/l
- Often used at much higher doses to achieve sleep in 45 seconds
  - Typically 350 mg/l at vaccination





…. Finquel vet. / Tricaine Pharmaq / Nytox vet.

- Powder formulation necessitates making a stem solution
- Should be buffered when used in FW
  - with equal amounts of $NaHCO_3$
- Rapid induction leads to little cortisol rise when used as an anaesthetic
- Has poor stress reducing capacities when used as a sedative

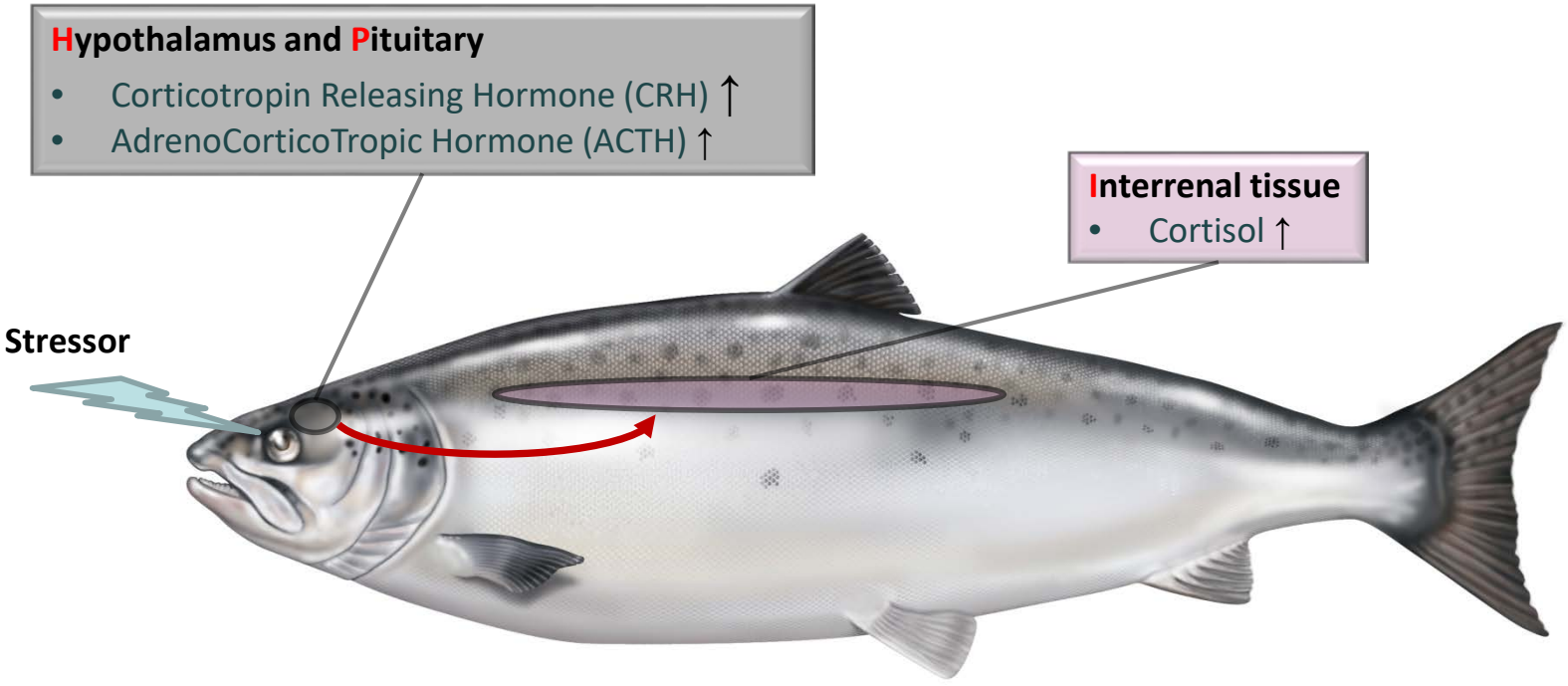
Benzoak vet.

- Benzocaine 200 mg/ml in propylene glycol
- Low water solubility
- Pharmacological properties much like tricaine, however:
  - Slightly slower induction
  - Reportedly somewhat lover safety margin at high temperatures
  - No stem solution or buffer needed
- SPC: doses up to 40 mg/l

Aquacalm vet.

- Metomidate hydrochloride powder 1000 mg/g
- No MRL or MA, not for use on food fish
- Recommended dose 5 mg/l
- Probably no analgesia
- Popular with researchers:
  - Fast induction & recovery
  - Does not elicit any cortisol rise
  - Perfect for blood sampling for cortisol/stress monitoring
- Probably poor stress reduction capacities

Stress physiology - «The HPI-axis»
Hypothalamic → Pituitary → Interrenal axis



Metomidate blocks cortisol low in the HPI-axis, directly on cortisol synthesis by enzyme inhibition in the interrenal cells

Thank you for your attention!